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BOTULINUM TOXIN IN MANAGEMENT OF BACK PAIN

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Abstract

Introduction
The botulinum toxin is a widely used therapeutic agent. It is used for aesthetic reasons in treatment of glabellar wrinkles. Therapeutic indications include cervical dystonia, hyperhidrosis or migraines. Also, it can be used in pain management, especially back pain. Back pain is one of the most common pain syndromes decreasing quality of life. Treatment involves various methods such as conservative and surgical approach. One of the methods is botulinum toxin.

Objectives
This article aims to evaluate usage, mechanism and treatment effects of back pain using botulinum toxin.

Methods
A Literature review of articles published in Pubmed between 2000 and 2024 using following words “botulinum toxin”, “botulinum”, “back pain” and “treatment”.

Results
Botulinum toxin injections are one of the pain management methods used especially in low back pain and myofascial pain syndrome. Treatment relies on its myorelaxant properties and inhibition of neuromodulator secretion such as substance P or acetylocholine. Pain relief effects are noted after three weeks and can last up to six months. In the initial stages a significant amount of patients report relief of pain.

Conclusion
Botulinum toxin is one of the treatment methods for lower back pain. It is a safe, minimally invasive and effective treatment. Patients can feel the relief even in three weeks and the effects might persist even up to six months.

Keywords: Botulinum toxin, botox, Low Back pain, myofascial pain syndrome, management, treatment
INTRODUCTION

Botulinum toxins (BoNTs) are proteins produced by bacteria of the genus Clostridium. Clostridia are anaerobic, gram-positive, spore-forming bacteria. The most common species include Clostridium botulinum, Clostridium baratii, Clostridium butyricum, and Clostridium argentinensis (Choudhury et al. 2021). Clostridium bacteria are widely found in the environment - in soil, water, and also colonize the gastrointestinal tract of humans and many animal species. BoNTs are metalloproteases, and their primary mechanism of action is the blockade of exocytosis at the neuromuscular junction (Kumar et al. 2016).

The history of modern botulinum toxin therapy dates back to the 1970s. In 1977, Alan B. Scott and Edward J. Schantz pioneered the use of botulinum toxin type A injections into extraocular muscles to treat strabismus (Erbguth et al. 2007). This was the first documented therapeutic use of BoNTA, then known as Oculinum©. The product name was changed to Botox© two years after its market introduction (Choudhury et al. 2021).

Currently, the applications of botulinum toxin are extensive - both therapeutic and aesthetic. Therapeutic indications include chronic migraine, upper limb spasticity, cervical dystonia, hyperhidrosis, strabismus, blepharospasm, and hemifacial spasm. Treating glabellar lines is the most popular aesthetic indication. The list of new indications for BoNT treatment is continually expanding, with pain management being an interesting application (Choudhury et al. 2021).

One of the most common pain syndromes is back pain. Approximately 75-85% of the population experiences an episode of back pain at least once in their lifetime (Milanov et al. 2014). It is one of the most frequent causes of sick leave and ranks sixth in the disability-adjusted life years (DALYs) metric (Hoy et al. 2014). It is most commonly located in the lumbar spine (Hoy et al. 2014, Wu et al. 2017) and is associated with risk factors such as office work, insufficient physical activity, and obesity (Casiano et al. 2023).

There are many methods of treating this pain, including patient education, physical activity, physiotherapy, and surgical treatment (Casiano et al. 2023). One of the newer minimally invasive methods is the treatment of spinal pain with botulinum toxin (Jabbari 2008, Safarpour and Jabbari 2018). The aim of our work is to discuss the application, mechanism, and effects of treating selected spinal pain syndromes with botulinum toxin.
MAIN PART
STRUCTURE OF BOTULINUM TOXIN

The botulinum toxin molecule consists of a core neurotoxin and a group of associated proteins. The core neurotoxin is composed of two protein chains - a light chain with a molecular mass of approximately 50 kDa, and a heavy chain with a mass of approximately 750 kDa. The chains are connected by a disulfide bond (Choudhury et al. 2021). Each botulinum toxin subtype is characterized by a different amino acid sequence in the chains.

The entire complex forming BoNT consists of three domains, each serving a different function at the molecular level. The first domain, located in the heavy chain, binds the toxin to cholinergic nerve endings at the neuromuscular junction. The second domain, also on the heavy chain, plays a crucial role in the translocation of the dissociated light chain into the cell cytoplasm. The third domain, located on the light chain, is a metalloprotease that degrades SNARE proteins (SNARE - soluble N-ethylmaleimide-sensitive factor attachment protein receptor), preventing vesicle fusion and acetylcholine (ACh) release, resulting in flaccid paralysis.

The auxiliary proteins protect the neurotoxin from low pH and protease digestion in the stomach (Carr et al. 2021).

TYPES OF BOTULINUM TOXIN

Seven types of botulinum toxin have been described, designated by consecutive letters of the alphabet from A to G. This classification is based on serological typing of the toxins, as each type is neutralized by specific antibodies (Choudhury et al. 2021).

Types BoNTA, BoNTB, BoNTE, and BoNTF are responsible for the development of botulism in humans. BoNTC and BoNTD additionally cause botulism in domestic animals (Matak et al. 2019). The various serotypes and subtypes also differ in their toxic and pharmacological properties.

BoNTA and BoNTB have the broadest therapeutic applications (Carr et al. 2021, Bellows and Jankovic 2019). In an updated Cochrane review, the single-use efficacy of BoNTA and BoNTB in treating cervical dystonia was shown to be similar, but BoNTB treatment was
associated with an increased risk of sore throat and dry mouth compared to type A. However, there is no clinical evidence favoring type A over type B toxin (Duarte et al. 2016).

**SIDE EFFECTS OF BOTULINUM TOXIN**

Botulinum toxin is widely used and is generally considered a safe therapy, with its safety and lack of long-term adverse effects confirmed by randomized controlled trials. However, as the list of indications grows, safety concerns arise. Reports of severe adverse events are sporadically reported, and data are based on case reports and spontaneous reporting systems. Adverse effects can occur with both aesthetic and therapeutic use of botulinum toxin but are more common with therapeutic use due to the dosage size, its diffusion at the injection site, and the target area (Yiannakopoulou 2015). The occurrence of adverse effects can be minimized through knowledge of the anatomy of the muscles undergoing therapy and the pharmacokinetics of the drug.

Severe known adverse effects include dysphagia, respiratory disorders, generalized muscle weakness, ptosis, pseudoaneurysm of the frontal branch of the temporal artery, necrotizing fasciitis, sarcoidal granuloma, Fournier's gangrene, cervical kyphosis, and anaphylactic shock.

**IMMUNOGENICITY OF BOTULINUM TOXIN**

BoNTs are proteins with immunogenic potential that can induce the production of antibodies. A rare complication of BoNT therapy is the formation of neutralizing antibodies, which reduce or eliminate the effectiveness of the therapy. Considering the immunogenic potential is particularly important in patients undergoing long-term BoNT therapy.

Factors increasing immunogenicity include higher doses, short intervals between therapeutic cycles, and a greater amount of antigenic protein in the preparation. Newer formulations without auxiliary proteins are associated with lower immunogenicity. The formation of neutralizing antibodies can be a clinical problem. To minimize this risk, safe intervals between injections and the use of the smallest effective dose in a given patient are recommended (Bellows and Jankovic 2019). Different BoNT formulations vary in their content of auxiliary proteins. Highly purified formulations with minimal auxiliary proteins show lower immunogenicity (Carr et al. 2021).
However, the results of a conducted meta-analysis indicate that the overall incidence of neutralizing antibody formation after BoNTA use is low (Rahman et al. 2022).

**CONTRAINDICATIONS IN THE USE OF BOTULINUM TOXIN**

Absolute contraindications include neuromuscular transmission disorders such as myasthenia gravis, Lambert-Eaton syndrome, hypersensitivity to the components of the preparation (lactose, human albumins), local skin infections, pregnancy, and allergy to botulinum toxin (Yiannakopoulou 2015). Contraindications also include the breastfeeding period; however, recent data indicate that the penetration of botulinum toxin into milk is unlikely with intramuscular administration at doses of 40-92 units (Drugs and Lactation Database 2024, Trivedi et al. 2017, Hudson et al. 2024). The use of certain medications may also constitute an absolute contraindication. These include aminoglycosides, aminoquinolones, D-penicillamine, cyclosporine, tubocurarine, pancuronium, gallamine, succinylcholine, lincomycin, tetracycline, polymyxin, and calcium channel antagonists. The aforementioned medications should be discontinued 10-14 days before botulinum toxin administration.

Relative contraindications include coagulation disorders and the use of anticoagulant medications (Yiannakopoulou 2015).

**DURATION OF BOTULINUM TOXIN ACTION**

Botulinum toxin exerts a prolonged effect on muscle relaxation, with the duration of action dependent on many factors. The reported duration of toxin effects ranges from 2 to 6 months (Wright et al. 2018). One of these factors is the type of botulinum toxin. Type A, which has the broadest therapeutic application, is characterized by a relatively long duration of action. The exact molecular mechanisms explaining the duration of therapeutic effect are individually variable and require further investigation (Kumar et al. 2016). The duration of action also depends on the administered dose, diffusion at the injection site, and the dilution used.

**EPIDEMIOLOGY OF SPINAL PAIN**

Spinal pain is a significant health problem affecting patients’ daily functioning and the quality of life (Hoy et al. 2014). It is localized in the cervical region in 4.9% of cases, while the most common location is the lumbar-sacral region, accounting for about 7.5% of cases (Hoy et
al. 2014, Wu et al. 2017). Based on the duration, we can distinguish acute pain, lasting less than 3 months, and chronic pain, lasting more than 3 months (Klimaszewska et al. 2011). For most patients experiencing both acute and chronic pain, a dynamic improvement in symptoms can be expected within six weeks. After this period, the rate of pain relief slows down [da C Menezes Costa et al. 2012]. Additionally, based on the cause, pain can be divided into nonspecific and specific. Nonspecific pain is characterized by a nonspecific origin, making its cause difficult to determine, and it occurs in approximately 90% of cases. The remaining 10% is specific pain, where the cause of the symptoms can be determined, such as discogenic pain or sciatica [Kuryliszyn-Moskal 2009].

PATHOMECHANISM AND TYPES OF PAIN

The mechanism of pain development is a multi-step process. It involves ascending pathways reaching the thalamus or cerebral cortex [Zylicz and Krajnik 2003]. Pain stimuli in the form of mechanical, thermal, or chemical signals (e.g., prostaglandins) are received by the nerve fibers endings. Subsequently, the pain fibers of the first-order neuron enter the spinal cord, where neurotransmitters such as substance P are released, and the pain signal is transmitted to higher nervous centers [da C Menezes Costa 2012, Osterweis et al. 1987]. The conduction of the pain signal can be directly inhibited by the action of botulinum toxin, particularly affecting the release of prostaglandins and substance P, which will be described in subsequent sections of the study [Safarpour and Jabbari 2018, Machado et al. 2016].

Spinal pain syndromes encompass a wide range of symptoms involving many diseases. Based on the causes, we distinguish mechanical, systemic, and referred pain etiology [Milanov 2014, Urits et al. 2019]. Given the significant number of types of spinal pain, this article will focus on the application of botulinum toxin in the treatment of lower back pain and myofascial pain syndrome.

The lower back pain can be divided into specific and nonspecific. Specific pain accounts for about 10% of cases and its cause can be determined, for example, intervertebral disc herniation, spinal canal stenosis, or trauma. In the remaining 90%, the pain is nonspecific, meaning its cause cannot be determined based on imaging studies (Hoy et al. 2014). The underlying pain is suggested to involve structural changes, such as intervertebral disc herniation, activating local inflammatory processes, and compressing nervous tissue, leading to the accumulation of pain neurotransmitters such as substance P or bradykinin. Another mechanism causing pain is ischemia. Excessive muscle contraction compresses blood vessels,
which can lead to ischemia and an anaerobic metabolism predominance in cells. This causes the accumulation of, among other things, lactic acid and hydrogen ions, promoting increased acidity of the environment. These signals are conducted by ascending nerve fibers through the posterior horns of the spinal cord to the thalamus and then to the cerebral cortex, where they are interpreted as pain (Jabbari 2008, Safarpour and Jabbari 2018, Machado et al. 2016, Romanelli et al. 2020).

Another condition presented in our study is myofascial pain syndrome. It is a syndrome characterized by a nonspecific inflammatory state located between the fascia and muscles, most commonly in well-muscled areas, such as the neck and lumbar-sacral spine [Li et al. 2023]. The definition of the syndrome also includes the presence of trigger points, which cause sensory and motor symptoms. Factors contributing to its development include poor posture, injuries, and excessive stress [Chochowska et al. 2012]. In the pathogenesis of pain, excessive production of acetylcholine is proposed, which promotes muscle spasticity, leading to the accumulation of nociceptive factors and inflammation. These mechanisms activate trigger points, which trigger the sensation of pain and cause a limitation of the range of motion [Leonardi et al. 2024].

MECHANISM OF ACTION OF BOTULINUM TOXIN

Each of the seven BoNT serotypes shares a common mechanism of action that prevents the release of neurotransmitters (primarily acetylcholine - ACh) at the neuromuscular junction. The ultimate effect is flaccid paralysis of the muscles [Godoy et al. 2016]. BoNT has the ability to form a lasting bond with the neuromuscular junction, but the paralysis of the target muscle is reversible - the transmission returns with the generation of new neuromuscular junctions.

A crucial aspect of BoNT’s action is the degradation of SNARE proteins, which are responsible for the fusion of cell membranes. This process is a key part of synaptic transmission, enabling the transfer of neurotransmitters through exocytosis. Botulinum toxin causes the fragmentation of SNAP-25 protein, which is essential for the release of ACh from presynaptic terminals. It also inhibits the release of other neurotransmitters such as substance P, neuropeptide Y, norepinephrine, dopamine, glycine, glutamate, and neurotransmitters associated with pain sensation. Neural conduction dependent on these transmitters is either disrupted or weakened. The inhibition of pain-related neurotransmitter release explains the
attempts to use BoNT in pain management [Safarpour and Jabbari 2018, Machado et al. 2016].


Similar to the treatment of lower back pain, botulinum toxin is used to directly act on the pathomechanisms of myofascial pain. By blocking the release of acetylcholine at the neuromuscular junction, it can inhibit its excessive production in myofascial pain. Furthermore, as in lower back pain, the mechanism of inhibiting substance P release is utilized, which interrupts pain transmission to the central nervous system [Safarpour and Jabbari 2018, Machado et al. 2016, Leonardi et al. 2024].

TREATMENT EFFECTS

The first study [Foster et al. 2001] indicating the effectiveness of botulinum toxin in the treatment of lumbar spine pain syndromes is a study from 2001, which examined the impact of botulinum toxin on 31 patients suffering from unilateral chronic lower back pain. Injections administered to 15 patients contained 40U of BoNT-A and were injected at 5 levels of the lumbar spine unilaterally into the extensor muscles, regardless of the location and extent of pain, while the remaining 16 patients received injections of saline solution. The results were assessed using the VAS scale and the Oswestry questionnaire. The Oswestry Disability Index (ODI) is one of the tools used to assess the level of disability in patients with spinal pain syndromes and associated limitations in various spheres of life. The questionnaire includes questions regarding: pain intensity, independence, lifting objects, walking, sitting, standing, sleeping, social life, sexual activity, and traveling. After 3 weeks, 86% of the patients receiving BoNT-A reported improvement in pain symptoms, while 73% reported a significant improvement of at least 50% on the VAS scale. In the placebo group, these percentages were 31% and 25%, respectively. After 8 weeks, 60% of patients in the BoNT-A group and 12.5% in the placebo group achieved a pain improvement on the VAS scale exceeding 50%. Regarding functionality assessed using the Oswestry questionnaire after 8 weeks, positive results were
reported in 66.7% of patients receiving botulinum toxin and 18.8% of patients receiving saline solution. No patient reported worsening of pain symptoms after botulinum toxin injections, unlike 2 patients in the placebo group.

In 2004 [Gallien et al. 2004], a clinical case was described involving the use of BoNT-A injections in a 21-year-old patient with cerebral palsy and paraspinal muscle dystonia in the lumbar region responsible for pain and hyperlordosis, whose treatment with oral muscle relaxants was ineffective. Injections of 200U BoNT-A were administered to paraspinal muscles at 6 sites. The results were positive; the patient experienced improvement in pain symptoms and dystonia frequency.

Another prospective study lasting 6 months [Ney et al. 2006] involved 60 patients: 18 women and 42 men aged 21 to 79 suffering from chronic lumbar pain. They received multiple injections of 500U of botulinum toxin A at once. Pain was assessed using the VAS scale, OLBPQ, and CLBPQ at the beginning of the study, after 3 weeks, 2 months, and 6 months. Significant improvement in pain symptoms occurred after 3 weeks in 60% of the patients and after 2 months in 58%. Effective response to the first injection was confirmed in subsequent doses in 94% of patients. Additionally, it was shown that the effects obtained after the first treatment cycle persisted up to the 4th month in 16.6% of patients and up to the 6th month in 8.3%. Two patients experienced flu-like symptoms after the first injections.

Another prospective study from 2006 [Jabbari et al. 2006], lasting 14 months, involved 75 patients with chronic lumbar spine pain. Injections of 40-50U of BoNT-A were administered to paraspinal muscles in the lumbar region at 4-5 sites, from L1 to S1 unilaterally or bilaterally. Each patient received from 200 to 500U at once. Repeat injections were administered after 4 months if pain symptoms persisted. The effects of BoNT-A injections were evaluated using the VAS scale, the number of days with pain, and the Oswestry scale on day 1, after 3 weeks, and at 2, 4, 6, 8, 10, 12, and 14 months of the study. After 3 weeks, 53% of patients and after 2 months, 52% of patients reported significant improvement in pain symptoms. Improvement was demonstrated in the evaluated scales at subsequent follow-up points compared to the parameters at the beginning of the study. Among patients who achieved positive results, subsequent treatment cycles were effective in 91% of them throughout the study period. Five percent of patients experienced flu-like symptoms lasting 2-5 days.

A randomized, single-blind, phase 3 trial from 2011 [Jazayeri et al. 2011] included 50 patients with chronic lower back pain. They received injections of 40U of BoNT-A or saline solution at 5 sites into paraspinal muscles. Pain effects were assessed using the VAS scale at the beginning of the study, at 4 and 8 weeks after injections, and functionality using the
Oswestry questionnaire at the beginning of the study and at 8 weeks after injections. In the 4th week, 76% of patients who received BoNT-A injections achieved a clinical response on the VAS scale compared to 20% of patients who received saline injections. In the 8th week, improvement was observed in 64% of patients receiving BoNT-A compared to 12% of patients in the placebo group.

In a newer study from 2016 [Machado et al. 2016], a group of 18 patients received unilateral or bilateral injections of 100U BoNT-A into extensor muscles in the lumbar spine, totaling from 500 to 1000U BoNT-A, while a group of 19 patients received injections of saline solution in the same areas. Results were assessed using the VAS scale and the Oswestry questionnaire. At 6 weeks, satisfactory effects (VAS <4) were not achieved; however, significantly more patients in the botulinum toxin group reported improvement in pain intensity reduction and overall functioning compared to the placebo group.

A double-blind, 3-phase trial from 2017 [Cogné et al. 2017] showed no significant difference in reducing lower lumbar spine pain between groups among 19 participants who completed the study, assessed at 30, 90, and 120 days of the study. Both groups received injections of 200U of botulinum toxin or placebo, and vice versa, at 120 days of the study.

In a prospective study from 2021 [Sahoo et al. 2021], 19 patients were assessed using the VAS scale, Roland-Morris disability scale, and Oswestry questionnaire at 4 weeks, 3 months, and 6 months from the beginning of the study. Intramuscular injections contained 100U of BoNT-A. Significant improvement in pain symptoms and patient functioning was demonstrated at each follow-up point, persisting up to 6 months after injection.

In summary, current literature justifies the use of botulinum toxin in the treatment of spinal pain syndromes. This therapy results in significant improvement in pain symptoms, especially in the short term. Additionally, it is more effective with higher doses of BoNT-A, and the effects can last for several months, while adverse effects are rare.

Table 1: Summary of Included Studies
<table>
<thead>
<tr>
<th>Study</th>
<th>Year of study</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Patient groups</th>
<th>BoNT-A dose</th>
<th>Treatment effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foster et al.</td>
<td>2001</td>
<td>Randomized trial</td>
<td>31</td>
<td>15 pts. BoNT-A</td>
<td>200 units</td>
<td>At 3 weeks: 86% reported improvement in pain; placebo group: 31% improvement</td>
</tr>
<tr>
<td>Gallien et al.</td>
<td>2004</td>
<td>Case report</td>
<td>1</td>
<td>all patients received BoNT-A</td>
<td>200U</td>
<td>Improvement in pain and dystonia after 1 month</td>
</tr>
<tr>
<td>Jabbari et al.</td>
<td>2006</td>
<td>Prospective Study</td>
<td>75</td>
<td>all patients received BoNT-A</td>
<td>200-500U</td>
<td>At 3 weeks: 53% improvement; at 2 months: 52% improvement</td>
</tr>
<tr>
<td>Ney et al.</td>
<td>2006</td>
<td>Prospective Study</td>
<td>60</td>
<td>All patients received BoNT-A</td>
<td>200-500U</td>
<td>At 3 weeks: 60% improvement</td>
</tr>
<tr>
<td>Jazayeri et al.</td>
<td>2011</td>
<td>Randomized trial</td>
<td>50</td>
<td>25 pt. BoNT-A</td>
<td>200-400 Ipsen unit</td>
<td>At 4 weeks: BoNT-A group: 76% pain improvement; placebo group: 20%</td>
</tr>
<tr>
<td>Machado et al.</td>
<td>2016</td>
<td>Randomized trial</td>
<td>37</td>
<td>18 pt. BoNT-A</td>
<td>500-1000 units</td>
<td>Significant improvement in pain after 6 weeks in BoNT-A group</td>
</tr>
</tbody>
</table>
CONCLUSIONS

Botulinum toxin, due to its inhibitory action on the release of neurotransmitters associated with pain perception and its muscle-relaxing effect, has found application in the treatment of conditions such as chronic migraine, upper limb spasticity, cervical dystonia, hyperhidrosis, strabismus, eyelid spasm, and hemifacial spasm. Additionally, by blocking the release of acetylcholine at the neuromuscular junction, excessive production of acetylcholine in musculoskeletal pain can be inhibited.

In the analysis of clinical studies in recent years, the use of intramuscular injections of botulinum toxin to reduce symptoms of lumbar spine pain syndromes also appears promising. This therapy demonstrates particular effectiveness with higher doses of BoNT-A, with its analgesic effect lasting for several months and minimal side effects. Furthermore, future actions should focus on increasing the number of patients in randomized trials, extending the observation period, and analyzing the cost-effectiveness of treatment to ensure broader application of toxin in the treatment of pain syndromes.
DISCLOSURE

Author’s contribution

Conceptualization: Bianka Nowińska, Katarzyna Słychan, Methodology: Blanka Łuczak, Izabela Hądzlik, Julia Biały-Karbowniczek Software: not applicable; Check: Klaudia Bulska, Patrycja Brzozowska, Andrzej Piela Formal analysis: Konrad Sławek Investigation: Jan Piotrowski, Bianka Nowińska Resources: Katarzyna Słychan Data curation: Patrycja Brzozowska, Julia Biały-Karbowniczek Writing - rough preparation: Izabela Hądzlik, Jan Piotrowski Writing - review and editing: Katarzyna Słychan, Blanka Łuczak Visualization: Klaudia Bulska, Andrzej Piela Supervision: Konrad Sławek, Bianka Nowińska Project administration: Blanka Łuczak Receiving funding: not applicable

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